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Randomised controlled trial of short term treatment to eradicate *Helicobacter pylori* in patients with duodenal ulcer

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Abstract

***Objective*—To determine whether one week's drug treatment is sufficient to eradicate *Helicobacter pylori* in patients with duodenal ulcer.**

***Design*—Single blind, randomised controlled trial.**

***Setting*—Specialised ulcer clinic in a teaching hospital.**

***Patients*—155 patients with *H pylori* and a duodenal ulcer verified endoscopically which had either bled within the previous 24 hours or was causing dyspepsia.**

***Interventions*—Patients were allocated randomly to receive either omeprazole for four weeks plus bismuth 120 mg, tetracycline 500 mg, and metronidazole 400 mg (all four times a day) for the first week (n=78), or omeprazole alone for four weeks (n=77). Further endoscopy was performed four weeks after cessation of all drugs.**

***Main outcome measures*—Presence or absence of *H pylori* (by urease testing, microscopy, and culture of antral biopsy specimens), duodenal ulcer, and side effects.**

***Results*—Eradication of *H pylori* occurred in 70 (95%) patients taking the four drugs (95% confidence interval 86% to 97%) compared with three (4%) patients taking omeprazole alone (1% to 11%). Duodenal ulcers were found in four (5%) patients taking the four drugs (2% to 12%) and in 16 (22%) patients taking omeprazole alone (14% to 32%). Mild dizziness was the only reported side effect (six patients in each group) and did not affect compliance.**

***Conclusions*—A one week regimen of bismuth, tetracycline, and metronidazole is safe and effective in eradicating *H pylori* and reduces the number of duodenal ulcers four weeks after completing treatment.**

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Introduction

The linking of relapse of duodenal ulcers with *Helicobacter pylori* has been a considerable advance in managing patients with ulcer disease. Several studies have shown that in patients with duodenal ulcer and *H pylori* eradication of *H pylori* during ulcer healing is followed by duodenal ulcer relapse in only 5-10% of patients after one year compared with around 85% relapse in patients without eradication.[1-3] The most effective regimens against *H pylori* usually consist of three drugs taken three to four times a day for between two and six weeks.[1-4] Patient compliance with such treatment regimens can be difficult. Furthermore, side effects increase with duration of treatment. For these reasons we performed a randomised controlled trial to investigate whether one week of treatment is sufficient to eradicate *H pylori*.

Patients and methods

We performed antral biopsies on all patients undergoing oesophagogastroduodenoscopy during a four month period at this hospital and found to have an active duodenal ulcer. We included patients with dyspeptic symptoms and also those with gastrointestinal bleeding from their duodenal ulcer. (Those with gastrointestinal bleeding had endoscopy within 24 hours of admission.) The biopsy specimens were tested for the presence of urease using a commercial kit (CLO test, Delta West, Western Australia). All patients with urease positive test results were considered for entry to the trial. Exclusion criteria were haemodynamic instability, previous surgery for acid reduction, and pregnancy. Once entered, patients were randomised by instructions in consecutively numbered sealed opaque envelopes to receive either omeprazole for four weeks, plus colloidal bismuth subcitrate 120 mg four times daily, tetracycline 500 mg four times daily, and metronidazole 400 mg four times daily for the first week, or omeprazole alone for four weeks. Drug treatment was started within 24 hours of endoscopy.

Eight weeks later (four weeks after all treatment had finished) the patients reattended the hospital. At this visit they were asked about any side effects they had experienced, followed by further endoscopy to look for ulcer healing. At the same time antral biopsies for microscopy, culture, and detection of urease were performed. The staff performing the endoscopic and bacteriological assessments were unaware of the drugs the patient had been taking.

Bacteriological techniques—Two antral biopsy specimens were minced aseptically and Gram stained to detect Gram negative spiral organisms. The minced tissue was cultured on Columbia agar (Oxoid) supplemented with 5% horse blood and incubated for five days under microaerophilic conditions. The identity of *H pylori* was confirmed by colony morphology, Gram stain, and positive biochemical test results (oxidase, catalase, and urease). Eradication of *H*

pylori was defined as failure to detect the organism by culture.

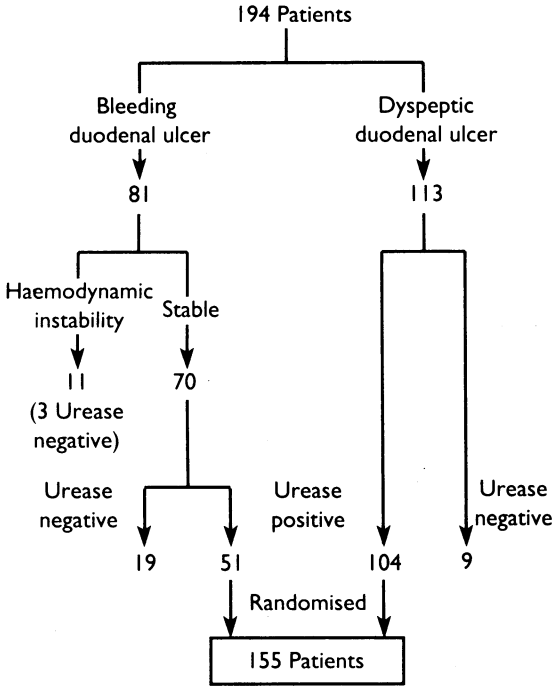
The trial was approved by this hospital's ethical committee, and all patients gave informed consent before participation in the trial. All statistical tests for significance were by χ^2 analysis. Confidence intervals were calculated with an exact formula.

Results

One hundred and ninety four consecutive patients with a confirmed duodenal ulcer underwent antral biopsy for detection of urease. The figure shows the details. A total of 155 patients with urease positive test results were suitable for entry and randomisation. The percentage of patients presenting with dyspepsia who had *H pylori* (92%) was significantly more than that of those presenting with bleeding who had *H pylori* (73%) ($p<0{\cdot}01$). Seventy eight patients were randomised to receive the four drug regimen (omeprazole, bismuth, tetracycline, and metronidazole in the first week, followed by omeprazole) and 77 to receive omeprazole alone. The patients were well matched with respect to age, sex ratio, and mode of presentation (table I).

Follow up was achieved in 74 (95%) patients receiving all four drugs and 72 (94%) patients taking omeprazole. Mild dizziness was reported by six patients in each group, but this did not affect compliance.

Endoscopy performed four weeks after completion of all treatment showed that four (5%) patients (95% confidence interval 2% to 12%) taking four drugs had a duodenal ulcer compared with 16 (21%) patients (14% to 32%) who were treated by omeprazole alone ($p<0{\cdot}01$). Most duodenal ulcers occurred in patients who had presented with dyspepsia rather than bleeding, but the trend was not significant (table II). Table II also shows the *H pylori* status of the 20 patients with duodenal ulcer at follow up.



Details of patients considered for entry into trial

TABLE I—*Details of patients randomised to receive omeprazole, bismuth, tetracycline, and metronidazole or omeprazole alone*

	Omeprazole, bismuth, tetracycline, and metronidazole	Omeprazole
No of patients	78	77
Median (range) age (years)	41 (16-72)	40 (17-84)
No (%) men	58 (74)	53 (69)
No (%) aged >40	40 (51)	36 (47)
No (%) with bleeding from duodenal ulcer	24 (31)	27 (35)
No (%) with dyspepsia	54 (69)	50 (65)

TABLE II—*Outcome in patients randomised to receive omeprazole, bismuth, tetracycline, and metronidazole or omeprazole alone*

	Omeprazole, bismuth, tetracycline, and metronidazole (n=78)	Omeprazole (n=77)
No of patients followed up	74	72
After treatment		
No (%) of patients cleared of *H pylori*	70 (95)	3 (4)
No (%) with duodenal ulcer	4 (5)	16 (22)
No with duodenal ulcer and positive for *H pylori*	1	16
No (%) of patients with duodenal ulcer presenting with bleeding	1 (1)	3 (4)

Eradication of *H pylori* was achieved in 70 (95%) patients (86%-97%) receiving all four drugs who were followed up compared with three (4%) of those patients (1% to 11%) who were taking omeprazole alone ($p<0{\cdot}001$). Of the patients in both groups whose biopsy specimens remained urease positive (n=72), in all but two was *H pylori* confirmed by microscopy and culture. Of the 74 patients who became urease negative, one was subsequently shown to be positive for *H pylori* by culture. Thus the urease test was 97% specific and 99% sensitive for detecting *H pylori* after treatment.

Data on ingestion of non-steroidal anti-inflammatory drugs were available for all patients who had bled from their duodenal ulcer. Eight patients (14%) who were positive for *H pylori* were taking these drugs at the time of their bleed compared with three (14%) who were negative for *H pylori*. Of the eight who were positive for *H pylori*, four were randomised to each group. All four patients given all four drugs became negative for *H pylori* compared with one patient given omeprazole. No patient taking non-steroidal anti-inflammatory drugs on admission had a duodenal ulcer at follow up.

Discussion

This trial provides good evidence that one week of bismuth, metronidazole, and tetracycline, in conjunction with omeprazole, is sufficient to eradicate *H pylori* in most patients. Our choice of drugs was based on current evidence indicating that the most effective regimens consist of bismuth, metronidazole, and either tetracycline or amoxycillin.[4] Possible hypersensitivity to amoxycillin made us choose tetracycline. A tetracycline derivative, doxycycline, was considered as it can be given twice daily and penetrates tissue better, but it seems to be less effective than tetracycline in eradicating *H pylori*.[5] The only side effect experienced was dizziness. As it occurred with equal frequency in both groups and is a recognised side effect of omeprazole[6] we attributed it to this drug, although a placebo effect is also possible.

The duration of treatment to eradicate *H pylori* has become progressively shorter since the first reports, in which six weeks' combination treatment was given.[1] The current consensus suggests that two weeks' treatment is sufficient,[4] but reports vary as to whether treatment against *H pylori* is given during the first or last fortnight of concomitant treatment with drugs to suppress acid secretion. We chose to give drugs active against *H pylori* during the first week of treatment for the sake of simplicity for the patient. Logan *et al* have reported experience of a one week regimen (bismuth, amoxycillin, metronidazole) in a heterogeneous group of patients (with duodenal ulcer, non-ulcer dyspepsia, and gastric ulcer).[7] Metronidazole was given on only the last three of the seven days. Although that was an

uncontrolled study, eradication of *H pylori* (measured by urea breath test) was achieved in 87% of their patients. Disturbance of taste was the most common side effect.

The different prevalence of *H pylori* in our patients with a bleeding duodenal ulcer (73%) as opposed to those with a non-bleeding duodenal ulcer (92%) has not been reported to date. Previous studies have recorded a consistently high *H pylori* colonisation rate in patients with duodenal ulcer—usually over 90%—but such patients have either a non-bleeding duodenal ulcer or patient details are not stated.[1-3 8] We observed that patients with recurrent duodenal ulcers may be divided loosely into those whose ulcer repeatedly bleeds and those whose ulcer repeatedly causes pain. It is impossible to say from our data whether the differing prevalences of *H pylori* observed between bleeding and non-bleeding duodenal ulcers are causally related or not. Until now, many (including the Sydney Working Party on *H pylori*)[4] consider bleeding duodenal ulcer as an absolute indication for treatment of *H pylori*. Our results suggest that this may not be the case, and we would urge *H pylori* status to be checked in this group of patients before starting treatment to eradicate *H pylori*.

The 16 duodenal ulcers found on follow up in 72 patients treated with omeprazole alone seems unexpectedly high. Normally omeprazole will heal around 95% of duodenal ulcers with four weeks of treatment. The likely explanation is that most patients' ulcers were healed, but as they had endoscopy four weeks after omeprazole was stopped, these ulcers represent early recurrences. A similar finding occurred in a study by Marshall *et al*, in which ranitidine gave unexpectedly low rates of healing[2]; the authors argued that the ulcers were most likely to be recurrences. We found far fewer ulcers in patients who had taken all four drugs. Eradication of *H pylori* seems to reduce early recurrence of duodenal ulcer, as well as recurrence over a longer one year follow up, as noted in previous trials.[1-3]

The ideal method of detecting *H pylori* remains controversial. Most agree that detection of urease in an antral biopsy of an untreated patient is diagnostic of *H pylori* infection. After treatment *H pylori* may be suppressed but not eradicated, and urease production might be so low as to be undetectable by urease tests. Microscopy and culture have been claimed as essential to check on *H pylori* status after treatment.[4] Culture remains the most specific means of identifying *H pylori*. Three of our patients had negative cultures and absence of urease but positive smears. Without a standard for detecting *H pylori* some studies (like ours) regard a positive culture as diagnostic of *H pylori*[1] whereas others regard either a positive smear or culture as diagnostic.[2] In our study the discrepancy between the two was very small and does not alter our conclusion concerning the effectiveness of our regimen. The tests performed after treatment to detect *H pylori* showed that urease activity alone correctly identified the *H pylori* status in virtually every patient. Other drug regimens have resulted in greater discrepancies between the tests, perhaps due to partial eradication of the organism, leaving insufficient numbers for detection by a technique based on biopsy. We believe that urease activity detected in an antral biopsy specimen after treatment with omeprazole, bismuth, tetracycline, and metronidazole, as described already, is sufficiently sensitive and specific to detect *H pylori* without the need for routine microscopy or culture, or both. However, new regimens should have full bacterial documentation to validate simple tests of detection.

In conclusion, we believe that regimens of more than one week to eradicate *H pylori* are no longer necessary. One week of bismuth, metronidazole, and tetracycline seems to be effective and safe and to have minimal side effects.

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Fibrinolytic balance and lupus anticoagulant in patients with repeated spontaneous fetal loss

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Recurrent pregnancy loss in women without genetic, anatomical, or hormonal abnormalities is sometimes characterised by placental infarction. It may be associated with lupus anticoagulant, which predisposes to fetal loss by mechanisms still to be defined.[1] Other risk factors include thrombocythaemia[2] and impaired fibrinolytic activity. This last condition is manifested by an imbalance between tissue plasminogen activator and its inhibitor plasminogen activator inhibitor, which is apparently not related to the presence of lupus anticoagulant.[3] To further investigate this problem we studied fibrinolytic balance in lupus anticoagulant positive and lupus anticoagulant negative women with a history of repeated spontaneous fetal loss.

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Patients, methods, and results

The study was carried out in 20 lupus anticoagulant negative women aged 26-43 (mean 33) years with two or more (range 2-4, mean 2·6) fetal losses occurring in the first (76%) or second (24%) trimester. We also studied 18 lupus anticoagulant positive women aged 23-41 (mean 31) years with two or more (range 2-6, mean 3) fetal losses occurring in the first (71%) or second (29%) trimester.

Patients were screened for systemic diseases, diabetes mellitus, chromosome abnormalities in a parent, uterine abnormalities, and endometrial or hormonal luteal phase defects. Thirteen of the lupus anticoagulant positive patients had systemic lupus erythematosus, diagnosed according to American